REMARKS

Claims 89-98 and 100-127 are pending in the application. Entry of the following remarks to the file are respectfully requested.

THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102

A. The Rejection under 35 U.S.C. § 102(b) Is In Error

Claims 89-98, 100-127 have been rejected under 35 U.S.C.§ 102(b) as being anticipated by Capecchi, 1989, Trends in Genetics, 5(3):70-76 ("Capecchi"). Applicants submit that the rejection is in error.

The Examiner alleges that the teachings of Capecchi encompass the use of a single inbred strain of animal as the source of both the flanking sequences of the targeting DNA construct and the targeted cells. Applicants respectfully disagree. Applicants believe that a brief summary of the general practice of the scientists in the field of gene targeting at the time of the invention would help one recognize the novelty of the present invention.

The Declaration of the inventor, Dr. Anton Berns, dated March 14, 1995 ("the Declaration"), submitted in the Amendment dated August 2, 2007, established that at the time of the invention, scientists in the field of gene targeting were using targeting DNA construct which was derived from a mouse strain that was different from the targeted cells. The scientists, intending to target a particular gene, would typically use a targeting DNA construct such as that derived from BALB/c or Black 6 mouse strains, whereas the targeted cells are from the 129 mouse strain (see paragraph 12 of the declaration). At the time of the invention, the scientists generally expected that increasing the length of the homologous region would increase the efficiency of gene targeting. The increase in efficiency was not believed to be related to the degree of sequence identity between the flanking sequence of the targeting DNA construct and the targeted cells (see paragraph 8 of the declaration). Only after disclsoure by the inventors of the present invention, for example, in Riele et al., 1992, Proc. Natl. Acad. Sci. USA 89:5128-5132 ("Riele"), did the practice of the scientists in the field started to change. A copy of Riele et al. is enclosed as Exhibit A.

The Examiner repeats in the advisory action that Capecchi's disclosure imply how to use the flanking sequence of the targeting DNA construct. In particular, the Examiner refers to Capeechi's statements "which gene to mutate and how to mutate" and "knowledge generated within the species or from other species". The first statement came from a paragraph that discusses the usefulness of gene targeting in genetic analysis of complex phenomena in

complex organisms:

> "We are no longer dependent on random mutagenesis to generate mutations. Through gene targeting, the potential now exists to generate mice of any desired genotype. The experimenter chooses both which gene to mutate and how to mutate it. The criteria for selecting which gene to mutate can be based on knowledge generated within the species or from other species." (Capecchi, page 70, left column, paragraph 3).

Here, Capecchi is describing the precision of the mutation within a gene that is afforded by gene targeting as compared to random mutagenesis. It says nothing about how to use the flanking sequences of the targeting DNA construct and of the targeted cells. The second statement refers to the broad applicabilty of gene targeting as a technique to any cloned mouse genes.

> "The application of this approach to mouse genetics is dependent on the availability of a cloned, genomic fragment of the chosen locus. At present this does not appear to be a limitation. The number of available cloned mouse genes that now exist is very large and new methods for isolating additional genes are continually being developed." (Capecchi, page 70, right column, paragraph 2).

Again, it says nothing about the genetic origins of the targeting DNA and the targeted cells. The two statements certainly do not teach or imply that the flanking sequence of the targeting DNA construct and the targeted cells are derived from the same inbred animal. Nor do they indicate how to use the flanking sequences of the targeting DNA construct and of the targeted cells.

In the Advisory Action, the Examiner combines the above statements with a snippet of Capecchi's discussion on the frequency of recombination to draw the following inference: "It would be preferred that the flanking sequence and the sequence at the genome of the targeted cells are the same, i.e. they are from the same inbred strain of animal, *because* Capecchi teaches that "the frequency of recombination between co-introduced DNA molecules is strongly proportional to the *extent of homology* between them."."(Page 2, lines 14-16 of the Advisory Action)(emphasis added).

However, Applicants submit that the term "extent of homology" in Capecchi does not refer to nucleotide sequence identity. Instead, the term "extent of homology" in Capecchi refers to the *length* of the homologous regions rather than to the degree of sequence identity. This is very evident in the two sentences immediately following Capecchi's mention of "extent of homology":

> "When DNA molecules share more than *5 kilobases of homology*, then nearly every molecule introduced into cell nucleus participates in at least one recombination event. Recombination between co-introduced DNA molecules

> can, however, be detected between molecules sharing *as little as 25-50 base pairs* of homology." (emphasis added; Capecchi, page 71, left column, lines 5-11)

It is clear that when Capecchi discusses the effect of the "extent of homology" on recombination frequency, he is referring to the *length* of the DNA that shares sequence homology. So there is nothing in Capecchi that discusses the level of nucleotide sequence identity. Furthermore, in paragraph 8 of the Declaration, it is stated that, in 1989 (same time period as the Capecchi publication cited herein), the skilled person in the art would regard the "extent of homology" to refer to the *length* of the regions of homologous DNA and not to the degree of sequence identity. The usage of this term in Capecchi cited by the Examiner is consistent with the statement in the Declaration. One of skill in the art would have understood that the extent of homology means the length of the regions of homologous DNA in Capecchi.

In view of the foregoing, Applicants respectfully submit that the Examiner's interpretation of Capecchi's disclosures is erroneous.

In the Advisory Action, page 2, lines 17-18, the Examiner states that the term "homologous recombination" means that the sequences recombine to each other have *very high* homology, and the *higher* the homology the merrier, i.e., 100% homology would be preferred. However, Applicants could not locate such a teaching anywhere in Capecchi. The term "homologous recombination" plainly states that the sequences that recombine need only be homologous to each other. As discussed above, Capecchi is not concerned with the degree of sequence identity between the targeting DNA and the targeted DNA. Capecchi does not disclose or suggest that very high homology or 100% homology is preferred for efficient gene targeting. The Examiner appears to be incorporating Applicants' disclosures into Capecchi, or relying on his own beliefs.

Applicants respectfully point out that it is recognized at the time of the invention that homologous recombination is different from the simple hybridization of DNA molecules (see discussions in paragraphs 15 (nucleation theory) and 10 (intramolecular recombination) of the Declaration), and thus there is no basis for the assumption that "the higher the homology the merrier". Moreover, as discussed in paragraph 9 of the Declaration, the term "maximization of homology" as used in a 1989 reference by Sedivy (also mentioned in paragraph 8) does not refer to maximizing sequence identity. In view of the foregoing, Applicants submit that there is no teachings or implication in Capecchi or in the knowledge at the time that very high homology or 100% sequence identity between the targetting DNA and targeted DNA is preferred in homolgous recombination.

In the Advisory Action, page 2, lines 25-35, the Examiner states three reasons for

maintaining the rejection in view of Applicants' earlier remarks and the Declaration. Applicants respectfully submit that the purpose of the Declaration is not to show what strains of mice were used in the process of making targeting DNA constructs. Rather, the Declaration points out that *prior to* the disclosure of the present invention, the scientific community did not appreciate the importance of using isogenic DNA vectors, and the general practice was to use targeting DNA construct and targeted cells from different mouse strains.

First, the Examiner alleges that the claims do not recite the inbred strain of animal has to be mouse strain 129 (page 2, lines 25-26). Applicants submit that the invention is not limited to using mouse strain 129 as the inbred strain of animal. All that is required, is that the flanking sequences of the targeting DNA construct and the targeted cells are from the same inbred strain of animal.

Secondly, the Examiner alleges that one of ordinary skill in the art at the time of the invention has already known to use the mouse strain 129 genomic library for preparing the targeting DNA construct because there were numerous requests for the mouse strain 129 genomic library (page 2, lines 26-28). In response, Applicants submit that in the absence of a compelling motivation such as that provided by the present invention, a scientist at the time of the invention would not have taken the special steps involving considerable time, effort and expense required to use targeting DNA and targeted cells from the same inbred strain for gene targeting. At the time of the invention, the scientists were all routinely using flanking sequence of the targeting DNA construct that were derived from a mouse strain that is different from the targeted cells (i.e., genomic DNA clone derived from BALB/c or Black 6 mouse strains and targeted cells from strain 129). Only after the disclosure by the inventors of the present invention, did the practice of the scientists in the field changed. Paragraphs 12 and 13 of the Declaration support the assertion that after the inventors' disclosure of the invention, scientists in the field became aware of the advantages of using flanking sequences of the targeting DNA construct and targeted cells from the same inbred strain. Moreover, the scientists in the field, instead of going through the labor of making the targeting DNA from the 129 strain mouse library, requested the genomic library made from mouse strain 129.

Thirdly, the Examiner alleges that Capecchi shows that the technology for preparing genomic DNA library and isolation of genomic fragment was known at the time of the invention and one of ordinary skill would know how to prepare and isolate genomic clone from the mouse strain 129 genomic library. Applicants submit that the Declaration is not meant to prove that one of ordinary skill in the art at the time of the invention does not know (i) how to prepare mouse strain 129 genomic library and (ii) how to isolate a genomic clone from said library. Rather, the requests discussed in the Declaration support the assertion that the

scientists, after realizing the importance of the present invention, changed their practices from what was taught earlier in Capecchi and quoted by the Examiner (i.e., using any available cloned genes from any mouse genomic DNA library for gene targeting, without regard to the genetic background of the targeted cells) to specifically matching the source of the flanking sequences of the targeting DNA construct and the targeted cells.

In view of the foregoing, Applicants request that the rejection of claims 89-98, 100-127 under 35 U.S.C.§ 102(b) as being anticipated by Capecchi be withdrawn.

B. <u>The Rejection under 35 U.S.C. § 102(e) Is In Error</u>

Claims 89-98 and 100-127 have been rejected as being anticipated by U.S. Patent 5,464,764 issued to Capecchi et al. (" the '764 Patent"). Applicants submit that the '764 patent fails to disclose each and every element of independent claim 89 and its dependent claims 90-98 and 100-127. The present invention is not anticipated because the '764 patent does not teach explicitly or inherently the use of a single inbred strain of animal as the sources of both the flanking sequences of the targeting DNA construct and the targeted cells.

The Examiner alleges that the teaching of the '764 Patent encompasses using targeting DNA sequence and the target DNA sequence both from the same source, i.e., from same mouse strain. The Examiner states that the term "substantially homologous" means that the sequences recombine to each other have very high homology, and the higher the homology the merrier, i.e., 100% homology would be preferred. Applicants submit that the '764 Patent does not define the term "substantially homologous" as stated by the Examiner. The '764 Patent states: "One hundred percent sequence homology is most preferred, however, lower sequence homology can be used to practice the invention. Thus, sequence homology as low as about 80% can be used" (col. 20, lines 36-39). The same rejection has been raised, and has been overcome, in the parent application Serial No. 09/253,818 in an Office Action dated January 6, 2003. Arguments similar to the response filed July 7, 2003 are presented below.

Applicants submit that the term "homology" convey a qualitative evolutionary relationship between sequences rather than a quantitative relationship.

> "Homology" has the precise meaning in biology of "having a common evolutionary origin", but it also carries the loose meaning of "possessing similarity or being matched". Its rampant use in the loose sense is clogging the literature on protein and nucleic acid sequence comparisons with muddy writing and, in some cases, muddy thinking. In its precise biological meaning, "homology" is a concept of quality." Reeck, 1987, Cell 50, 667 ("Reeck").

A copy of Reeck is enclosed as Exhibit B. (Reference C45 in Information Disclosure Statement submitted November 24, 2003). Applicants respectfully request that the Examiner

takes this into account when examining the usage of the term in the '764 Patent. The term "homology" is used in the '764 Patent to convey the evolutionary relationship between targeting DNA and target DNA. In this context, 100% homology means that the targeting DNA are from the same animal species as the target DNA. The usage of this term in the '764 Patent can be gleaned from Figure 4 and the brief description for Figure 4 at column 6, lines 25-28, which states that:

> FIG.4 is a graphic representation of the absolute frequency of homologous recombination versus the amount of 100% sequence homology in the first and second DNA sequences of the PNS vectors of the invention.

The x-axis of Figure 4 is labeled HOMOLOGY (KB) from 0 to about 14 KB. At column 21, lines 9-14, the '764 Patent states that in Figure 4 the absolute frequency of targeting events is plotted as a function of "the number of kilobases of Hprt sequence contained within the positive-negative selector ("PNS") vectors. See Capecchi, M. R. (1989) Science 244: 1288-1292."("Capecchi 1989") A copy of Capecchi 1989 is enclosed as Exhibit C (Reference C07 in Information Disclosure Statement submitted November 24, 2003). Accordingly, the "amount" as used in the brief description refers to the "number of kilobases", and the "100% sequence homology" refers to the relationship between the Hprt sequences in the PNS vector (targeting DNA) and in the ES cell (target DNA). However, a closer reading of the experimental details underlying the experiment portrayed in Figure 4 indicates that the targeting DNA and target DNA are respectively derived from two different strains of mouse. The details of this experiment can be inferred from Capecchi 1989[1]. Applicants submit and one of skill in the art would recognize that it is not likely that the 14 Kb of genomic sequences in the two different strains of mouse used by Capecchi 1989 are base-by-base 100% identical[2].

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[1] Figure 4 of the '764 Patent is taken from the authors' earlier publication, Fig. 3 of Capecchi 1989, which portrays the same experiment in which targeting vectors containing varying lengths of Hprt DNA are used to target the Hprt gene in mouse ES cells. Capecchi 1989 refers to an earlier publication, Thomas and Capecchi, 1987 Cell 51:503-512 ("Thomas"), for further details regarding inactivation of Hprt (page 1289, first column, fourth paragraph, first sentence and second col. first full paragraph, second sentence). Thomas describes an experiment in which targeting vectors containing different lengths of Hprt DNA are used to disrupt an endogenous Hprt gene. The reference discloses that the target Hprt DNA is from mouse C57Bl/6 ES cells, whereas the targeting Hprt DNA is from the mouse ARK line (see p.511, first column, second paragraph, first sentence, and fifth paragraph, first sentence).

[2] To illustrate this point, Applicants refer to page 30 of the specification and Figure 2 of the instant application which analyzed the sequence divergence between the 129 strain and another BALB/c strain in the Rb locus. Numerous differences were identified in the 10.5 Kb region analyzed.

There is no evidence to suggest that the entire 14 Kb Hprt sequences from the two different mouse strains had been sequenced, compared, and shown to be 100% identical. Therefore, Applicants contend that the '764 Patent would not have used the term "100% sequence homology" in the brief description of Figure 4 and in the specification to describe targeting DNA and target DNA that are not known and not likely to be 100% identical. Rather, the '764 Patent uses the term "100% sequence homology" to describe an evolutionary relationship (the precise meaning of the term according to Recce), i.e., target DNA and targeting DNA that are DNA sequences of the same gene from the same species of animal (e.g., mouse). This is the only consistent interpretation of the term permitted in the '764 Patent specification and his supporting data in the working example. One of skill in the art would have interpreted the '764 Patent as simply teaching the use of targeting and target DNA from the same species of animal.

In an example provided in the '764 Patent (column 22, lines 53-54), the construction of the targeting DNA was carried out as described in Thomas (Reference C60 in Information Disclosure Statement submitted November 24, 2003) (Exhibit D). In Thomas, the target DNA and flanking sequences of the targeting DNA construct were obtained from a gene library made from the genomic DNA of cells from the mouse ARK cell line. The targeted cells used in the '764 patent were derived from mouse line C57BL/6 or CC1.2 (col. 23, lines 40-63). Clearly, the flanking sequences of the targeting DNA construct and the targeted cells in the '764 patent were not derived from the same inbred animal as recited in the present claims. Therefore, the '764 patent does not teach the limitation that the targeting DNA construct and the targeted cells are derived from the same inbred animal.

Moreover, it is clear as discussed above, that the term "substantially homologous" and "100% homologous" in the '764 Patent do not *necessarily* mean substantial nucleotide sequence identity or 100% nucleotide sequence identity. Thus, the '764 Patent does not inherently anticipate the claim invention.

In view of the foregoing, Applicants request withdrawal of the rejection based on the '764 Patent.

IV. REJECTION BASED ON NONSTATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 89-98, 100-127 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-23 of U.S. Patent No. 6,653,113 to Berns ("the '113 patent") and claims 1-18 of U.S. Patent No. 5,789,215 ("the '215 patent") to Berns. In response, while not admitting that the claims of the above-identified patent application are not patentably distinct from claims 1-23 of the '113

patent or claims 1-18 of the '215 patent, Applicants, upon indication of allowable subject matter, will submit a Terminal Disclaimer under 37 C.F.R. § 1.321(c) for the above-identified application.

CONCLUSION

Entry of the foregoing amendments and consideration of the foregoing remarks are respectfully requested. No fee is believed to be due for this amendment. Should any fee be required, please charge such fee to Jones Day Deposit Account No. 50-3013. Applicants respectfully submit that all claims are now in condition for allowance. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining issues.

Respectfully submitted,

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